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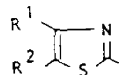
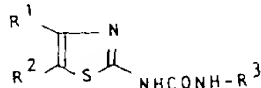
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(54) THIAZOLYLUREA DERIVATIVES, PROCESS FOR THEIR PREPARATION, AND MEDICINAL COMPOSITION CONTAINING SAME.

(57) Novel thiazolyl derivatives represented by the following general formula:



wherein R¹ represents a lower alkyl group or a substituted or unsubstituted phenyl group, R² represents a hydrogen atom, a lower alkyl group, a lower alkoxy group or a lower alkylthio group, and R³ represents a pyridyl group, an isoxazolyl group or a group represented by

a process for their preparation, and a medicinal composition containing same which has an immunity-controlling effect and is useful against chronic articular rheumatism, viral diseases, cancer, etc.

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TITLE MODIFIED

see front page

S P E C I F I C A T I O N

Title of Invention

Thiazolylurea derivatives, a process for preparing same and a pharmaceutical composition containing same

Technical Field

This invention relates to novel thiazolylurea derivatives, processes for preparing same and medicinal compositions containing same.

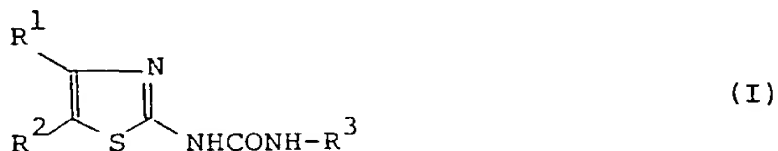
More particularly, this invention relates to thiazolylurea derivatives which possess immuno-modulating activity and are thus therapeutically effective against immunodiseases such as chronic rheumatoid arthritis and are also useful against viral diseases or for the immunotherapy of cancers, processes for preparing same and medicinal compositions containing same.

A number of steroid-type and nonsteroid-type anti-inflammatory drugs have heretofore been clinically employed against autoimmune diseases such as rheumatism. However, these drugs are not quite satisfactory in their pharmacological effects, side effects and toxicity. The present inventors have carried out an extensive research on chemical substances, which give a peculiar effect to cells that take part in an immunity response and act to modulate the immunity response

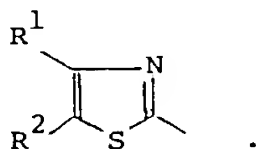
of the host. As a result, they have succeeded in obtaining thiazolylurea derivatives which are extremely desirable as medicines having excellent immuno-modulating activity but little toxicity.

Disclosure of Invention

The present invention provides thiazolylurea derivatives as new chemical substances which are represented by the general formula:



wherein R^1 stands for a lower alkyl group or a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom, a lower alkyl, lower alkoxy or lower alkylthio group, and R^3 for a pyridyl or iso-oxazolyl group or a grouping of the general formula:



Illustrative of the representative compounds of the thiazolyl derivatives represented by the above general formula (I) in connection with the present invention are as follows:

N,N'-bis(4-methylthiazol-2-yl)urea;
N,N'-bis(4-methyl-5-methylthiazol-2-yl)urea;
N,N'-bis[4-methyl-5-(n-propyl)thiazol-2-yl]urea;
N,N'-bis(4-phenylthiazol-2-yl)urea;
N,N'-bis[4-(p-methylphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-methylphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-methylphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(p-chlorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-chlorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-chlorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(p-methoxyphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-methoxyphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-methoxyphenyl)thiazol-2-yl]urea;
N,N'-bis[4-(p-nitrophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-nitrophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-nitrophenyl)thiazol-2-yl]urea;
N,N'-bis(5-methyl-4-phenylthiazol-2-yl)urea;
N,N'-bis(5-methoxy-4-phenylthiazol-2-yl)urea;
N,N'-bis(5-methylthio-4-phenylthiazol-2-yl)urea;
N,N'-bis[4-(p-fluorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-fluorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-fluorophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(p-dimethylaminophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(m-dimethylaminophenyl)thiazol-2-yl]urea;
N,N'-bis[4-(o-dimethylaminophenyl)thiazol-2-yl]urea;

N,N'-bis[4-(p-methylthiophenyl)thiazol-2-yl]urea;
 N,N'-bis[4-(m-methylthiophenyl)thiazol-2-yl]urea;
 N,N'-bis[4-(o-methylthiophenyl)thiazol-2-yl]urea;
 N-(2-pyridyl)-N'-(4-phenylthiazol-2-yl)urea;
 N-(3-pyridyl)-N'-(4-phenylthiazol-2-yl)urea;
 N-(4-pyridyl)-N'-(4-phenylthiazol-2-yl)urea; and
 N-(5-methylisoxazol-2-yl)-N'-(4-phenylthiazol-2-yl)urea.

As the new compounds of the present invention show tautomerism between their amine-form and their imine-form, the compounds of the present invention include all of these tautomers.

A first process provided by the present invention to prepare the novel compounds of this invention is characterized by reacting a 2-aminothiazole having the general formula:



wherein R^1 and R^2 have the same meanings as defined above, with phosgene or a chloroformate represented by the general formula:



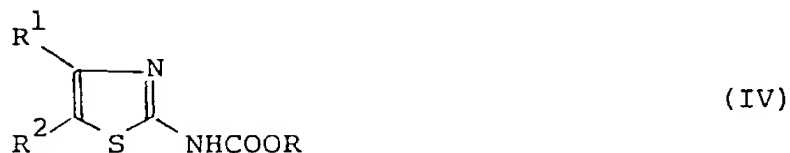
wherein X stands for a chlorine atom or a lower alkoxy group,

a benzyloxy group or a substituted or unsubstituted phenoxy group. The reaction can be carried out by either dissolving or suspending a starting material represented by the general formula (II) which may optionally be in the form of a suitable acid addition salt in a solvent and then adding dropwise or in a similar manner a compound of the general formula (III) to the solution or suspension. As utilizable solvents, may be mentioned, for example, benzene, toluene, xylene, dioxane, 1,2-dimethoxyethane, tetrahydrofuran, and N,N-dimethylformamide. For the purpose of removing hydrogen chloride which will be produced in the course of the reaction, it may be possible to use an organic base such as pyridine or triethylamine or an inorganic base such as sodium carbonate, potassium carbonate or sodium hydrogen carbonate.

This reaction may proceed at temperatures below room temperature. However, it is possible to heat the reaction mixture to a temperature in the range of from room temperature to the boiling point of the solvent to accelerate the reaction.

The 2-aminothiazoles represented by the general formula (II) as starting materials are known compounds and are described in detail, for example, in technical publications [Jacques V. Metzger, ed. "The Chemistry of Heterocyclic Compounds", Vol. 34; "Thiazole and Its Derivatives", Part Two, (1979)].

The present invention also provides as a process for preparing the novel compounds represented by the general formula (I) a method in which an N-thiazolylylcarbamate represented by the general formula:



wherein R^1 and R^2 have the same definitions as given above and R stands for a lower alkyl group, a benzyl group or a substituted or unsubstituted phenyl group, is reacted with an amine having the general formula:



wherein R^3 has the same meaning as defined above. This reaction can generally be carried out by mixing two starting compounds respectively represented by the general formulas (IV) and (V) in a solvent such as tetrahydrofuran, dioxane, benzene, xylene, 1,2-dimethoxyethane or N,N-dimethylformamide. The reaction temperature may be chosen at will within a temperature range of from room temperature to the boiling point of the solvent. The reaction is usually completed in 1-10 hours.

The latter method is particularly advantageous for the preparation of thiazolylylurea derivatives of the general

formula (I) in which R^3 is other than thiazolyl group.

The above compounds represented by the general formula (I) have valuable pharmacological activity. It is worthy to mention specially that these compounds have excellent immuno-modulating activity. Since they have a low degree of toxicity, they are extremely useful as medicines.

The pharmacological activity of the compounds of the present invention was confirmed as follows.

Various test systems using animals have been routinely adopted for the determination of immunopotentiative action. Results of reinforcement tests of the delayed hypersensitivity, which are considered to be the most representative ones among such known test systems, will hereinafter be described as follows.

The delayed hypersensitivity induced on a mouse when picryl chloride (2-chloro-1,3,5-trinitrobenzene) is coated on the skin of the mouse is known as a typical cellular immunity. This is one of test systems commonly adopted throughout the world [see Asherson, G.L. and Ptak, W. "Contact and Delayed Hypersensitivity in the Mouse - I. Active Sensitization and Passive Transfer", Immunology, 15, 405-416 (1968)].

This test system was used for the reinforcement tests of the delayed hypersensitivity.

Test Example 1 Reinforcement Test of Delayed Hypersensitivity

Test Procedures:

One group of eight ICR male mice, each having a body weight of about 30 g or so, were used for the test.

Sensitization was effected by coating a 3% solution of picryl chloride in a 4/1 mixture of olive oil and acetone on the shaved abdomen of each of the mice.

Simultaneously with the sensitization, a solution or suspension of a compound of the present invention dissolved or suspended in a 0.2% solution of carboxymethylcellulose in a physiological saline was orally administered to the mouse at a dose of 50 mg per Kg of its body weight. To each mouse of a control group, was similarly administered a 0.2% carboxymethylcellulose solution in a physiological saline.

The delayed hypersensitivity was challenged 7 days after the sensitization by pinching each of the pinnae of each mouse with a pair of forceps whose tip portions were wrapped with a felt impregnated with a 1% solution of picryl chloride in olive oil and coating the pinnae with the solution. The thickness of each pinna was measured before the challenging and 24 hours after the challenging and the ratio of increase of the thickness (average value of both of the pinnae of the eight mice) is shown in Table 1.

For comparison, a similar test was carried out using Levamisole hydrochloride. Its results are also shown.

F.t tests were carried out on the thus-obtained test

results. Any group in which the test results were superior to those of the control group at significance levels of $P < 0.05$ and $P < 0.01$ are marked up by an asterisk(*) and double asterisks(**) respectively.

Results:

When the compound of the present invention was administered simultaneously with sensitization, the delayed hypersensitivity caused by a challenging was reinforced. The reinforcement effect of the compound of the present invention was recognized to be comparative with or higher than that attained by Levamisole which was used for the sake of comparison.

Thus, it is considered that the compounds of the present invention have an effect of modulating the cellular immunity response (immuno-modulating activity) in mice.

Table 1

Reinforcement Tests
of Delayed Hypersensitivity


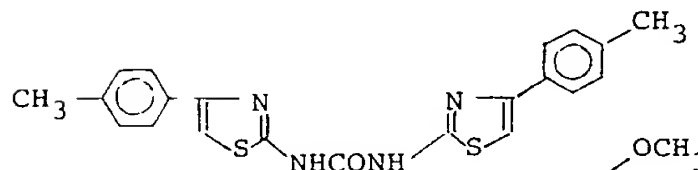

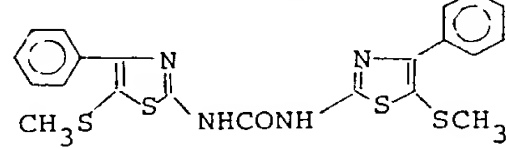
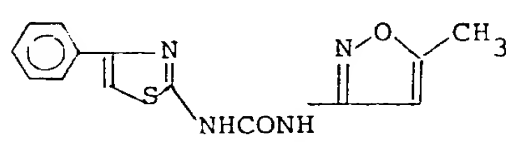
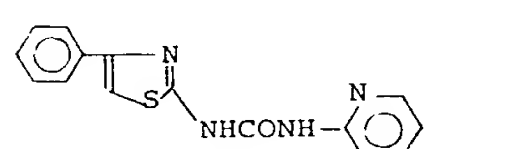
<u>Compound</u>	<u>Ratio of Increase of</u> <u>Pinna Thickness (%)</u>
	37.5*

Table 1 (Cont'd)

Reinforcement Tests
of Delayed Hypersensitivity

<u>Compound</u>	<u>Ratio of Increase of</u> <u>Pinna Thickness (%)</u>
	36.1**
	31.7*
	29.0
	37.8**
	25.4
Levamisole·HCl	31.2*

The adjuvant arthritis in rats caused by the injection of a Mycobacterium tuberculosis adjuvant is often utilized for a model test of chronic rheumatoid arthritis in human.

The mechanism of manifestation of this disease has not completely been elucidated, but it is known that the cellular

immunity plays an important role. The immuno-modulating activity of the compounds of the present invention was investigated in accordance with this known adjuvant arthritis test.

Test Example 2 Adjuvant Arthritis Test (Table 2)

Test Procedures:

8-Weeks-old SD male rats were used for the test. In 0.1 ml of fluid paraffin, 0.4 mg of dry dead cells of *Mycobacterium tuberculosis* were suspended, and the suspension was injected under the heel skin of the right hind leg of each rat. Each of the compounds of the present invention was subcutaneously administered 9 times in total before and after the injection of the adjuvant. Each of the compounds of the present invention was dissolved or suspended in a 0.2% solution of carboxymethylcellulose in physiological saline and administered to each rat at a dose of 5 mg per Kg of the body weight. The swollen volume of the left hind leg was measured during the period of from the day of injection to the day of completion of the test, and the swelling ratio was calculated. For comparison, a similar test was conducted using Levamisole hydrochloride. F.t tests were carried out on the test results obtained. Any group in which the test results were superior to those of a control group administered with a 0.2% solution of carboxymethylcellulose in physiological

saline at significance levels of $P < 0.05$ and $P < 0.01$ are marked up by an asterisk(*) and double asterisks(**), respectively.

Results:

The secondary inflammation of the adjuvant arthritis was remarkably suppressed by the compounds of the present invention. Their effects were statistically significant over the control group.

It was recognized that they exhibited an activity comparative with or stronger than that of Levamisole used for comparison. Thus, the compounds of the present invention are considered to have immuno-modulating activity and anti-arthritic activity.

Table 2

Adjuvant Arthritis Test

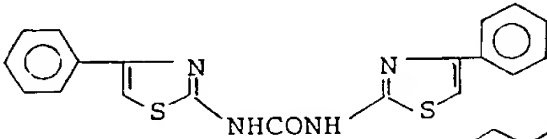
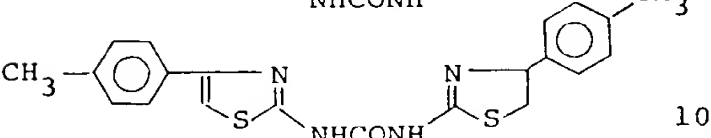
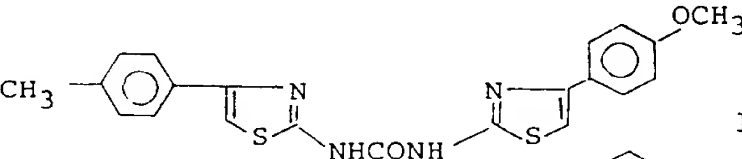
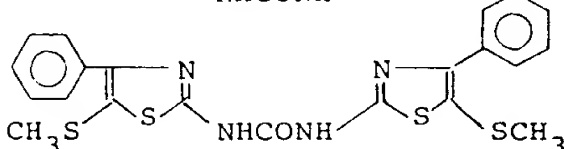

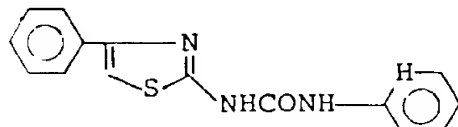
<u>Compound to be tested</u> (shown by formula)	<u>Number of cases</u>	<u>Swell suppression ratio to control group(%) (average value from 16th to 20th days)</u>
 <chem>c1ccc(cc1)/C(S)=N\NC(=O)N/C(S)=N/c2ccccc2</chem>	10	35.7*
 <chem>Cc1ccc(cc1)/C(S)=N\NC(=O)N/C(S)=N/c2ccc(C)cc2</chem>	10	29.3*

Table 2 (Cont'd)

<u>Compound to be tested</u> (shown by formula)	<u>Number of cases</u>	<u>Swell suppression ratio to control group(%) (average value from 16th to 20th days)</u>
	10	37.5**
	10	28.8*
	10	26.6
	10	34.6*
Levamisole·HCl	44	19.8*

As illustrated in Tests 1 and 2, the compounds of this invention have excellent immuno-modulating activity. Thus, they are effective for the remedy of diseases accompanied by reduction or abnormal change of immune functions, for example, autoimmune diseases such as chronic rheumatoid arthritis.

A toxicity test on the effective ingredients of certain medicines according to this invention will now be described

below as Test 3.

Test Example 3 Acute Toxicity Test through Oral Administration

Test Procedures:

To each of a group of five ddY male mice, was orally administered a medicine dissolved or suspended in physiological saline. They were watched for 7 days after the administration and an estimated LD₅₀ value was obtained.

Results:

The estimated LD₅₀ value of the effective ingredient of a medicine according to this invention was 1,000 mg/Kg or higher. This value is far greater than the estimated LD₅₀ value of Levamisole.HCl, the latter value ranging 200-300 mg/Kg. Therefore, the toxicity of the compound of the present invention is considered to be low.

Although the compounds of this invention may be used in the form of their free base as a raw material for preparing a medicinal composition when the compounds are applied as a medicine, it is preferable to use the compounds in the form of a pharmaceutically acceptable salt thereof, considering stability and ease for formulating it into a preparation and, particularly, where solubility in water is required such as in an injectable formulation.

The medicine according to this invention may be administered in the same preparation form and by the same adminis-

tration method as conventional immuno-modulating agents and carcinostatic substances. For instance, as an orally administrable preparation, it may be used in the form of capsules, granules, pills, fine grains, tablets or syrup. For administering through the rectum, it is suitable to prepare the medicine into suppositories. For injection, it may be applied subcutaneously, intramuscularly or intravenously.

As diseases to which an immuno-modulating activity of the new compounds of this invention can be applied, there may be mentioned diseases accompanied by an abnormal change of immune functions, for example, chronic rheumatoid arthritis; autoimmune diseases such as polymyositis; various infectious diseases; and a wide variety of cancers. It is expected that the immuno-modulating agent of the present invention would normalize the immune functions of patients affected by such diseases.

It is desirable to choose a suitable administration method and an appropriate preparation form for a medicine according to this invention depending on the type of disease and conditions of each patient. In case of oral administration, the dose of the compound of the present invention is 0.5 to 100 mg, preferably 1 to 30 mg per Kg of the body weight per day. In case of administration to the rectum, the dose is suitably 1 to 100 mg per Kg of the body weight

per day, while, in case of intravenous administration, the dose is preferably 1 to 10 mg per Kg of the body weight per day. Where it is administered subcutaneously or intramuscularly, the dose of the compound of the present invention is preferably 1 to 30 mg per Kg of the body weight per day. It is preferred that these doses be appropriately adjusted according to the type of diseases and the conditions of each patient. The therapeutic effect of the effective ingredient of the present invention may be increased, depending on the type of disease and the conditions of a patient, by using other medicines in combination. For example, when chemotherapeutic agents for cancers, such as alkylating agents and antimetabolites, which have a side effect of reducing the immunizing capacity of patients, are administered, the manifestation of such side effect may be prevented and their therapeutic effect may be synergistically increased if the effective ingredient of the present invention is used in combination.

Examples of this invention will hereinafter be described.

Example 1

Into 50 ml of a dry pyridine solution containing 7.5 g of 2-amino-4-phenylthiazole, 4.8 g of phosgene was absorbed under cooling (about 5°C). The temperature of the mixture was then allowed to rise to room temperature. To this solution, 7.5 g of 2-amino-4-phenylthiazole was added further. The mixture was stirred overnight. The pyridine was removed under reduced pressure and the residue was converted to powder in methyl alcohol. The powder was then recrystallized from an N,N-dimethylformamide/methyl alcohol mixed solvent to obtain 8.5 g of N,N'-bis(4-phenylthiazol-2-yl)urea.

Melting point: 285-287°C

Elementary analysis values as $C_{19}H_{14}N_4OS_2$:

	C	H	N	S
Calc. (%)	60.30	3.73	14.80	16.92
Found (%)	60.42	3.76	14.98	16.87

IR, $\nu_{\text{KBr}}(\text{cm}^{-1})$: 3330, 3200, 3100, 1720, 1705, 1670, 1590, 1570, 1540, 1500, 1450, 1340, 1310, 1270, 1190, 1080, 910, 865, 830, 780, 710

NMR, $\delta_{\text{TMS}}^{\text{DMSO-d}_6}$ (ppm): 7.2-8.0 (10H, m), 7.57 (2H, s), 10-11 (2H, bs: disappeared with D_2O)

Example 2

In 50 ml of tetrahydrofuran, was dissolved 5.7 g of 2-amino-4-p-methylphenylthiazole. The solution was cooled to 0-5°C, followed by addition of 2.6 g of ethyl chloroformate and 2.6 g of triethylamine. The mixture was stirred at room temperature for 1 hour and then for 2 hours at the reflux temperature of tetrahydrofuran. And insoluble matter was removed from the reaction mixture through filtration. The filtrate was concentrated under reduced pressure and the residue was crystallized using N,N-dimethylformamide to obtain 2.5 g of N,N'-bis[4-(p-methylphenyl)thiazol-2-yl]urea.

Melting point: above 300°C

Elementary analysis values as $C_{21}H_{18}N_4OS_2$:

	C	H	N	S
Calc. (%)	62.04	4.46	13.78	15.78
Found (%)	62.14	4.43	13.85	16.08

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 2.34 (6H, s), 7.2-7.8 (8H, m), 7.48 (2H, s), 10.8 (2H, bs: disappeared with D_2O)

Example 3

Into 45 ml of o-xylene, were added 1.5 g of ethyl N-(4-phenyl-2-thiazolyl)carbamate and 4.0 g of 2-aminopyridine. The mixture was stirred for 2.5 hours under refluxing. The reaction solution was allowed to stand for cooling. Deposited

crystals were collected by filtration and washed with methyl alcohol. The crystals were then recrystallized from an N,N-dimethylformamide/methyl alcohol mixed solvent to obtain 1.2 g of N-(2-pyridyl)-N'-(4-phenylthiazol-2-yl)urea.

Melting point: 247-249°C

Elementary analysis values as $C_{15}H_{12}N_4OS$:

	C	H	N	S
Calc. (%)	60.79	4.08	18.90	10.82
Found (%)	60.66	3.92	18.82	10.81

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 7.0-8.0 (9H, m), 8.39 (1H, d), 9.92 (1H, s), 12.22 (1H, s: disappeared with D_2O)

Following the procedures of Examples 1 - 3, the compounds of the following examples were obtained from their corresponding starting materials.

Example 4

N,N'-Bis[4-(p-methoxyphenyl)thiazol-2-yl]urea

Melting point: 288-292°C

Elementary analysis values as $C_{21}H_{18}N_4O_3S_2$:

	C	H	N	S
Calc. (%)	57.52	4.14	12.78	14.62
Found (%)	57.42	4.09	12.72	14.67

NMR, $\delta_{\text{TMS}}^{\text{DMSO-d}_6}$ (ppm): 3.8 (6H, s), 7.0-7.8 (8H, m), 7.4 (2H, s)

Example 5

N,N'-Bis[4-(p-chlorophenyl)thiazol-2-yl]urea

Melting point: 290-300°C

Elementary analysis values as $\text{C}_{19}\text{H}_{12}\text{Cl}_2\text{N}_4\text{OS}_2$:

	C	H	Cl	N	S
Calc. (%)	51.01	2.70	15.85	12.52	14.33
Found (%)	51.06	2.63	15.83	12.37	14.37

NMR, $\delta_{\text{TMS}}^{\text{DMSO-d}_6}$ (ppm): 7.45 (4H, d), 7.63 (2H, s), 7.90 (4H, s),
10.84 (2H, bs: disappeared with D_2O)

Example 6

N,N'-Bis[4-methyl-5-(n-propyl)thiazol-2-yl]urea

Melting point: 273.5-274.5°C

Elementary analysis values as $\text{C}_{15}\text{H}_{22}\text{N}_4\text{OS}_2$:

	C	H	N	S
Calc. (%)	53.22	6.55	16.55	18.95
Found (%)	53.47	6.58	16.56	18.86

Example 7

N,N'-Bis[5-methyl-4-phenylthiazol-2-yl]urea

Melting point: 254-256°C

Elementary analysis values as $C_{21}H_{18}N_4OS_2$:

	C	H	N	S
Calc. (%)	62.04	4.46	13.78	15.78
Found (%)	61.94	4.49	14.00	15.71

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 2.50 (6H, s), 7.35-7.65 (12H, m)

Example 8

N,N'-Bis[5-methylthio-4-phenylthiazol-2-yl]urea

Melting point: 207-210°C

Elementary analysis values as $C_{21}H_{18}N_4O_4S_2$:

	C	H	N	S
Calc. (%)	53.59	3.85	11.90	27.25
Found (%)	53.62	4.01	11.76	27.24

Example 9

N-(5-methylisoxazol-2-yl)-N'-(4-phenylthiazol-2-yl)urea

Melting point: 212-220°C

Elementary analysis values as $C_{14}H_{12}N_4O_2S$:

	C	H	N	S
Calc. (%)	55.99	4.03	18.65	10.68
Found (%)	56.01	4.07	18.75	10.62

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 2.4 (3H, s), 6.62 (1H, s), 7.3-7.6 (5H, m),
7.93 (1H, d), 9.74 (1H, s), 10.70 (1H, s:
disappeared with D_2O)

Example 10

N,N'-Bis[4-(m-chlorophenyl)thiazol-2-yl]urea

Melting point: 265-268°C

Elementary analysis values as $C_{19}H_{12}Cl_2N_4OS_2$:

	C	H	Cl	N	S
Calc. (%)	51.01	2.70	15.85	12.52	14.33
Found (%)	50.84	2.84	15.79	12.32	14.01

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 7.6-8.2(10H, m), 11.32(2H, br: disappeared with D_2O)

Example 11

N,N'-Bis[4-(m-methylphenyl)thiazol-2-yl]urea

Melting point: 254-256°C

Elementary analysis values as $C_{21}H_{12}N_4OS_2$:

	C	H	N	S
Calc. (%)	62.98	3.02	13.99	16.01
Found (%)	62.55	3.13	13.57	15.81

NMR, $\delta_{TMS}^{DMSO-d_6}$ (ppm): 2.40(6H, s), 7.1-7.8(10H, m), 11.0(2H, br: disappeared with D_2O)

Example 12

N,N'-Bis[4-(m-nitrophenyl)thiazol-2-yl]urea

Melting point: 273-276°C

Elementary analysis values as $C_{19}H_{12}N_6O_5S_2$:

	C	H	N	S
Calc. (%)	48.71	2.58	17.94	13.69
Found (%)	48.71	2.48	17.70	13.48

Example 13

N,N'-Bis[4-(p-fluorophenyl)thiazol-2-yl]urea

Melting point: 229-302°C

Elementary analysis value as $C_{19}H_{12}F_2N_4OS_2$:

	C	H	F	N	S
Calc. (%)	55.06	2.92	9.17	13.52	15.47
Found (%)	54.93	2.81	9.29	13.47	15.27

Example 14

N,N'-Bis[4-(p-dimethylaminophenyl)thiazol-2-yl]urea

Melting point: 263-266°C (decomp.)

Elementary analysis value as $C_{23}H_{24}N_6OS_2$:

	C	H	N	S
Calc. (%)	59.46	5.21	18.09	13.80
Found (%)	59.39	5.22	17.94	13.85

Example 15

N,N'-Bis[4-(p-methylthiophenyl)thiazol-2-yl]urea

Melting point: 283-284.5°C

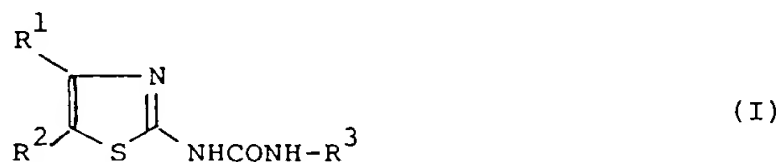
Elementary analysis value as $C_{21}H_{18}N_4OS_2$:

	C	H	N	S
Calc. (%)	53.59	3.85	11.90	27.25
Found (%)	35.62	3.75	11.88	26.95

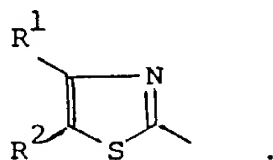
NMR(δ -DMSO- d_6 ppm): 2.52(6H, s), 7.54(2H, s), 7.24-7.92
(8H, m), 10.90(2H, br: disappeared
with D_2O)

CLAIM

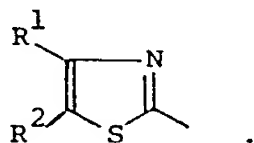
1. Thiazolylurea derivatives of the general formula:



wherein R^1 stands for a lower alkyl group or a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom, a lower alkyl, alkoxy or alkylthio group, and R^3 for a pyridyl or iso-oxazolyl group or a grouping of the general formula:



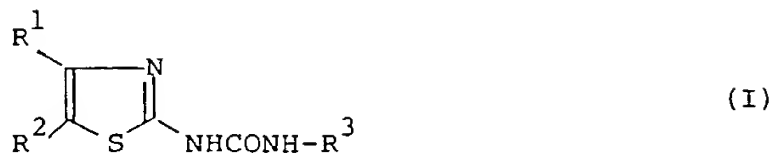
2. A compound according to claim 1, wherein, in the above general formula (I), R^1 stands for a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom and R^3 for a 2-pyridyl, 5-methyl-2-oxazolyl group or a grouping of the general formula:



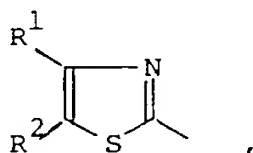
3. A process for the preparation of thiazolylurea

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derivatives of the general formula:



wherein R^1 stands for a lower alkyl group or a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom, a lower alkyl, alkoxy or alkylthio group, and R^3 for a pyridyl or iso-oxazolyl group or a grouping of the general formula:



characterized by reacting a 2-aminothiazole of the general formula:

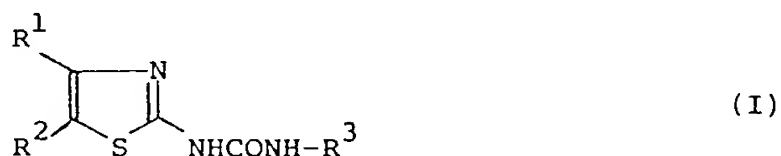


wherein R^1 and R^2 have the same definitions as given above, with phosgen or a chloroformate of the general formula:

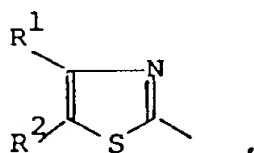


wherein X stands for a halogen atom, a lower alkoxy group, a benzyloxy group or a substituted or unsubstituted phenoxy group.

4. A process for the preparation of thiazolylurea derivatives of the general formula:



wherein R^1 stands for a lower alkyl group or a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom, a lower alkyl, alkoxy or alkylthio group, and R^3 for a pyridyl or iso-oxazolyl group or a grouping of the general formula:



characterized by reacting an N-thiazolylcarbamate of the general formula:



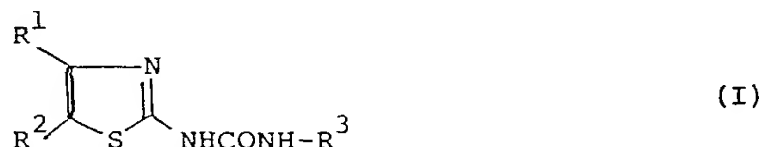
wherein R^1 and R^2 have the same definitions as given above

and R stands for a lower alkyl group, a benzyl group or a substituted or unsubstituted phenyl group, with an amine of the general formula:

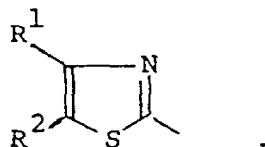


wherein R^3 has the same definition as given above.

5. A pharmaceutical composition possessing immuno-modulating activity, characterized by containing as an effective ingredient a thiazolylurea derivative of the general formula:



wherein R^1 stands for a lower alkyl group or a substituted or unsubstituted phenyl group, R^2 for a hydrogen atom or a lower alkyl, alkoxy or alkylthio group, and R^3 for a pyridyl or iso-oxazolyl group or a grouping of the general formula:



6. A pharmaceutical composition possessing immuno-modulating activity according to claim 5, wherein the thiourea

derivative is combined with a pharmaceutically acceptable diluent or carrier.

7. A pharmaceutical composition possessing immuno-modulating activity according to claim 5, wherein the composition is used for the remedy of chronic rheumatoid arthritis.

8. A pharmaceutical composition possessing immuno-modulating activity according to claim 5, wherein the composition is used for the immuno-therapy of cancers.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/JP82/00021 0069784

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. ³ C07D 277/48, C07D 277/54, C07D 417/12, A61K 31/425, A61K 31/44		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System :	Classification Symbols	
I P C	C07D 277/38 - 277/48, C07D 277/54, A61K 31/425, A61K 31/44, C07D 417/12	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched *		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No. ¹⁸
A	JP,A, 47-29531 (Chevron Research Co.) 6. November. 1972 (06.11.72)	1 - 8
A	JP,A, 54-61172 (Pierre Fabre S.A.) 17. May. 1979 (17.05.79) & US, A, 4225610 & FR, A, 2406634	1 - 8
A	JP,A, 54-154764 (Faizer Inc.) 6. December. 1979 (06.12.79) & US, A, 4217355	1 - 8
A	JP,A, 54-160369 (Faizer Inc.) 19. December. 1979 (19.12.79) Claim	1 - 8
A	JP,A, 52-125164 (Stauffer Chemical Co.) 20. October. 1977 (20.10.77) & US, A, 4027031 & DE,A, 2708327 & FR, A, 2348206	1 - 8
<p>* Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search :		Date of Mailing of this International Search Report :
April 5, 1982 (05.04.82)		April 26, 1982 (26.04.82)
International Searching Authority :		Signature of Authorized Officer ¹⁹
Japanese Patent Office		

Form PCT/ISA/210 (second sheet) (October 1977)



